Original Contribution

FOLLOW-UP OF HIGH-INTENSITY FOCUSED ULTRASOUND TREATMENT FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Abstract—Nonsurgical therapies have become treatment options for hepatocellular carcinoma (HCC). This study was to evaluate the efficacy and complications of high-intensity focused ultrasound (HIFU) treatment for patients with HCC. Between May 2001 and May 2005, 145 patients with HCC were enrolled for treatments using a HIFU tumor therapeutic system. Clinical symptoms, hepatic functions and values of serum α-fetoprotein (AFP) were tested before and after HIFU treatment. The changes in computerized tomography (CT) and magnetic resonance imaging (MRI), complications and survival time after HIFU were also obtained for further analysis. Symptoms improved or pain was relieved in 84.8% of the 145 patients and the rate of serum AFP decrease was 71.7%. The size of the target tumor shrank by various degrees. The 2-year survival rate was 80% in patients with stage Ib HCC, 51.4% in stage IIa and 46.5% in stage IIIa. During HIFU treatment, complications included body temperature increase and abnormal cardiac rhythm. After HIFU procedures, there were skin burns of different grades. In conclusion, HIFU is safe and effective for patients with hepatocellular carcinoma; HIFU can improve the survival quality of patients with HCC. (E-mail: xugl@mail.sysu.edu.cn) © 2011 World Federation for Ultrasound in Medicine & Biology.

Key Words: High-intensity focused ultrasound (HIFU), Hepatocellular carcinoma (HCC), Follow-up.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a prevalent malignancy and one of the deadliest cancers in China. Until now, surgical intervention remains the only curative therapy for HCC. However, about 80% of HCC patients in China are not suitable for surgical resection either because of the disease’s advanced stage or the presence of underlying cirrhosis (Kong et al. 2001; Wu et al. 1999). Therefore, nonsurgical therapies have become treatment options for HCC.

High-intensity focused ultrasound (HIFU) is a noninvasive treatment method that precisely targets tumor tissues without skin incision. HIFU focuses an extracorporeal ultrasound (US) source on a specific target tissue inside the body (Visioli et al. 1999). The US energy passes harmlessly through overlying tissues enroute to a tightly focused target area. The rapid rate of energy deposition generates a rapid temperature rise, which results in irreversible cell death with a defined region of tissue necrosis (Wu et al. 2002; Xu et al. 2005). Madersbacher et al. found that only five to seven layers of cells existed between necrosis and normal tissue, marking HIFU therapy safe and accurate (Madersbacher et al. 1998).

HIFU has been approved for clinical therapies of solid tumors or other diseases in liver, kidney, pancreas, rectum, prostate, breast, bone, skin and uterus (Chen et al. 2002; Guan and Liu 2006; Leslie and Kennedy 2006; Li et al. 2003; Wang et al. 2003; Wu 2006; Wu et al. 2006). Research indicates that HIFU has the advantage of being noninvasive, safe, effective and allows for quick recovery. Therefore, HIFU has a broad scope in the application of cancer therapy. In the early 1990s, some researchers started studies of HIFU therapies that target HCC. They showed that HIFU could evidently decrease the proliferation of these cancer cells and the tumor destruction rates were 76.3% ± 16% after one procedure and 94.2% ± 7.3% after two procedures.
Thirty-two patients had multiple lesions (two lesions in 21 patients, three lesions in eight and four lesions in three); the remaining 113 patients had one solitary lesion. The tumor size was described using its maximum dimension measured two-dimensionally on computerized tomography (CT) or magnetic resonance imaging (MRI) images. Tumor diameters ranged from 3 to 15 cm.

Prior to the HIFU treatment, 39 patients had negative levels of serum α-fetoprotein (AFP), 106 patients had positive AFP levels, which ranged from 27.9 to 12.1 \( \times 10^3 \) ng/mL. Thirty-eight patients had AFP levels from 25 to 400 ng/mL, 91 patients from 400 to 10 \( \times 10^3 \) ng/mL and 15 patients higher than 10 \( \times 10^3 \) ng/mL. The AFP levels were consistent with previous observations that not all HCCs secrete AFP and serum AFP concentrations are normal in up to 20% of HCC patients (Chabner et al. 2007).

According to the clinical tumor, node, metastasis (TNM) classification, 15 patients corresponded to stage II, 25 to IIIA, 42 to IIIB, 40 to IIIC and 23 to IV (including IVA and IVB). The patients presented with various symptoms (Table 1) and their pretreatment hepatic function classifications are shown in Table 2. The University Ethics Committee approved this study and each patient signed an informed consent.

**Instrument**

The JC-HIFU therapy system (Fig. 1) is manufactured by the Chongqing Haifu Technology Company, China. The focused US is produced by a transducer operating at the frequencies of 0.8 or 1.6 MHz, the focal length ranges from 100 to 135 mm. The peak US power is from 160 to 240 W and the maximum peak ultrasound intensity is 15,000 W/cm\(^2\). This system is equipped with a real-time ultrasonic monitor situated at the center of the HIFU transducer and the monitor frequency is 2.5–3.5 MHz. The transducer can be moved horizontally, whereas the treatment couch can move vertically so that conformal tumor coverage can be achieved.

**Treatment procedures**

To improve the effect of HIFU therapy, some synthesized therapies prior to HIFU are important. Some reports (Jin et al. 2003; Zhang et al. 2009) suggest that

<table>
<thead>
<tr>
<th>Table 1. Symptom relief after HIFU treatment</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Before HIFU</td>
</tr>
<tr>
<td>Disappear</td>
</tr>
<tr>
<td>Relief</td>
</tr>
<tr>
<td>Rate</td>
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HIFU = high-intensity focused ultrasound.
transarterial chemoembolization (TACE) therapy could largely decrease the blood supply to the tumor and the deposit of iodized oil could change the internal environment to increase the tissue’s absorption of US energy. In TACE procedures, we conducted percutaneous femoral artery puncture using the Seldinger technique. A guidewire was first inserted into the femoral artery through a hollow needle and then a sheath was passed over the guidewire under the guidance of X-ray fluorescence. A drainage tube was advanced through the sheath into selected feeding arteries of a tumor. Arteriography was then performed to show the distribution of the feeding arteries and tumor blood vessels. Chemotherapy drugs (Pirarubicin 60 mg/m², Mitomycin 14 mg/m², Fluorouracil 750 mg and Leucovorin 200 mg) were injected into the tumor-feeding arteries through the tube. Percutaneous ethanol injection (PEI) was similar to TACE except that pure ethanol and iodized oil were injected instead. For HCC with full blood supply, we performed the TACE therapy while for HCC with absent blood supply we locally injected ethanol or ethanol plus iodized oil. We treated 68 patients with TACE and 28 patients with PEI. It was possible that both TACE and PEI were applied on the same patient.

HIFU treatment was performed under general anesthesia, with the patient positioned prone or in the right lateral position. Routine examinations and preoperative preparations were conducted according to the principle of surgery. Twelve patients whose HCC was in the diaphragm were injected with 750–1000 mL saline solution in the right thoracic cavity. The US covering focus depended on the tumor size and the depth of the tumor under the body surface. If the tumor size was less than 5 cm or the tumor depth was less than 10 cm, the entire targeted region would be covered by HIFU. For larger tumors, HIFU covered the surface that would develop coagulation necrosis and a second treatment was arranged 20 to 30 days after the first therapy. Since there were differences in terms of tumor volume, depth and blood supply, it was difficult to decide in advance on the specific therapy dose or treatment time interval for each patient. During the HIFU procedure, real-time US imaging showed perceivable gray-scale increase in the targeted lesion. Treatment time with focused ultrasound depended on the tumor size, location, depth and blood supply. It was determined by experienced physicians that sufficient therapy dose was delivered when the visualized changes in the gray scales of US image was larger than 5 (typically the changes ranged from 12 to 16 gray-scales with a whole range of 256). In this study, the target tissue was exposed to acoustic focal peak intensities from 5000 to 15,000 W/cm². The scanning speed ranged from 1–3 mm/s and the track length was 20 mm by changing the focal length. High-intensity focused US treatment time ranged from 45 min to 2.5 h (median 1.3 h) with possible breaks. After HIFU, patients received supportive therapy and were observed in hospital for 3 to 15 days.

Follow-up of patients

All patients were followed up for 2 to 60 months to determine long-term efficacy and complications related to the therapy. Patients were arranged to visit the hospital at least twice and at most 11 times. The endpoints of the follow-ups were recurrence and death. Patients who responded to the HIFU treatment and who survived for long periods were provided with imaging studies on CT and MRI scanners. Dynamic contrast-enhanced MRI is the most suitable method of analyzing the targeted lesion, which is also an important method of follow-up studies (Klotz et al. 1997). Hynynen et al. (Hynynen et al. 1993) reported that the T2-weighted MR images could clearly show areas of necrosis and the margin between the necrotic and the surrounding normal tissues. Our MRI studies followed the methods established by the above investigators. Specifically, a Signa Excite II 1.5 T (General Electric Company, Fairfield, CT, USA) or a T5-II 0.5 T (Philips, Eindhoven, The Netherlands) MRI scanner was used in the patient imaging studies. Axial imaging sequences were T1WI (TR 450 ms, TE 15 ms), T2WI (TR 3600 ms, TE 85 ms), number of excitations 2~6, 90° RF pulse, slice thickness/gap 5.0 mm/0.5 mm, matrix size 196~256 × 256, FOV 370 mm. Contrast agent Gd-DTPA was administered at 0.2 mL/kg. The arterial phase scan was performed at 25 s and the venous phase scan at 55~65 s after contrast injection. The imaging volume extended from the top of diaphragm to

Table 2. Hepatic function distributions (patient number for each stage) before and after HIFU

<table>
<thead>
<tr>
<th></th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>81</td>
<td>48</td>
<td>16</td>
<td>145</td>
</tr>
<tr>
<td>After</td>
<td>81</td>
<td>46</td>
<td>18</td>
<td>145</td>
</tr>
</tbody>
</table>

HIFU = high-intensity focused ultrasound.
the inferior border of the liver. All follow-ups were completed by the end of May 2009.

**Statistical analysis**

Continuous variables were presented as the mean ± standard deviation (SD). Student’s t-test and the chi-square ($\chi^2$) test were used for evaluations of these variables. SPSS software 10.0 for windows (SPSS Inc., Chicago, IL, USA) was used for data analysis (Wang et al. 2011). The difference was considered statistically significant when the p-value was less than 0.05.

**RESULTS**

**Short-term efficacy**

The observed results of symptom relief are shown in Table 1. Abdominal pain relief was the most evident, which could be nearly 90%. Other conditions such as abdominal distension, fatigue and appetite loss were also improved but the effects on bloating and jaundice were less obvious.

No significant differences of routine blood test before and after HIFU could be found in all patients ($p = 0.73$). In general, serum alanine aminotransferase levels slightly increased after 1 week but slowly decreased after 1 month. The constituent ratio of hepatic function was not evident after one month of HIFU therapy ($p > 0.05$), which is shown in Table 2. Post-HIFU serum AFP levels decreased significantly compared with those before HIFU and the total decrease rate was 71.7% for the 106 patients who had high AFP levels before the HIFU treatment. Among these, 24 patients reduced to normal, 52 reduced to about half of the original level, 24 had no obvious change and the other six significantly increased ($p < 0.01$).

After HIFU treatment, reduced tumor blood supply and changes in imaging signals suggested coagulation necrosis in the tumor volume. Of all the patients, 34 (23.4%) patients had total tumor necrosis, 43 (29.7%) patients had a necrosis area larger than 75% of the tumor, 29 (20%) larger than 50%, another 39 patients (26.9%) were less than 50%. Figures 2, 3 and 4 show different responses to the HIFU treatment among some patients.

**Complications**

During HIFU treatment, there were complications of body temperature increase and abnormal cardiac rhythm.

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**Fig. 2.** The left figure of magnetic resonance imaging (MRI) shows a solid tumor appearing hyperintense in the right lobe, with a diameter of 10 cm before high-intensity focused ultrasound (HIFU). The right figure shows that 1 month after HIFU, the surface of tumor developed coagulation necrosis and its internal was not hyperintense.

**Fig. 3.** Patient, male, 55-years-old, with metastatic hepatocellular carcinoma (HCC) after surgery of sigmoid colon cancer. The left figure of magnetic resonance imaging (MRI) showed the metastatic HCC located in the right lobe, which was $5 \times 4$ cm before high-intensity focused ultrasound (HIFU). The right figure showed that the tumor disappeared half a year after HIFU therapy.
Minor skin burns at operation spots occurred in most of the patients: grade 1 in 37.2% of patients, grade 2 in 31.7% and grade 3 in 2.1%, respectively. Reactive effusion from the right pleural cavity was observed in seven patients but all these patients recovered within 2 weeks. Injuries of sternal vertebrae and vertebrae lumbales were found in three patients, probably caused by the effects of US when targeting the bigger or deeper tumors. Two patients had acute cholecystitis 1 day after HIFU therapy, since the tumors were close to the gallbladder. There were no other severely adverse events throughout the study.

Long-term efficacy

The prognosis of patients after HIFU mainly depended on the clinical stage and tumor necrosis area of HCC, which are indicated in Table 3. Survival appeared significantly better in patients with low stage HCC, where HIFU could target the whole tumor area \( (p < 0.05) \), as indicated in Figure 5.

Reasons of death

The reasons for patient death after HIFU therapy are listed in Table 3.

DISCUSSION

In the present study, post-HIFU serum AFP levels decreased significantly in all patients who had high levels before HIFU and many patients could maintain a normal level for long periods. One patient in our study lived for more than 5 years post-HIFU. After HIFU therapy, real-time US imaging showed obviously increased gray-scales in the targeted lesion, corresponding mainly to the extent of the coagulation necrosis.

Our study found that the prognosis of patients after HIFU depended on the TNM stage and hepatic function. Since most of the patients in our study were in higher stages and not suitable for surgical ablation, effects of HIFU targeting at low stages of HCC could not be compared with the surgical treatment.

The main reasons of death after HIFU application include cachexia, hepatic function loss or bleeding of the upper digestive tract. Although HIFU could effectively destruct tumor tissue and largely preserve hepatic function, it is incapable of preventing the harm of cirrhosis. However, for patients with advanced stage HCC, HIFU might be an effective palliative therapy.

Although HIFU is a noninvasive therapy, it has some complications such as skin burns or local pain (Li et al. 2009). Our data show that one major complication during the HIFU therapy was the local skin burn. Skin burn is caused by the heat cumulating in the skin during HIFU treatment and it is associated with the treatment time and ultrasound intensity. Although observed among the majority of patients, usually skin burn is not a severe complication and doesn’t require special intervention following the HIFU procedures. To prevent skin burns, skin changes should be intensively monitored, the therapy time interval could be prolonged if necessary and the temperature of the instrument should be maintained at no higher than 20°C by its cooling system.

### Table 3. Reasons for death after HIFU therapy

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Dyscrasia</th>
<th>Hepatic function failure</th>
<th>Bleeding</th>
<th>Fracture</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>45</td>
<td>51</td>
<td>20</td>
<td>5</td>
<td>24</td>
<td>145</td>
</tr>
<tr>
<td>Percentage</td>
<td>31.0%</td>
<td>35.2%</td>
<td>13.8%</td>
<td>3.4%</td>
<td>16.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

HIFU = high-intensity focused ultrasound.
The main complications caused by HIFU therapy also include body temperature increase and abnormal cardiac rhythm. To protect the patients, we set forth the following guidelines: When the body temperature is higher than 38°C or the cardiac rhythm is greater than 120 times per minute, the therapy should be stopped. Other minor complications such as acute cholecystitis or injuries of sternal vertebra and vertebrae lumbales, which occurred during the initial stage of our work, might not happen in the future with increasing experience.

In conclusion, HIFU ablation achieved satisfactory long-term efficacy and is safe for the treatment of advanced HCC. With less invasion and wider indications, HIFU could both target HCC tumors and protect hepatic function. More studies, especially large scale randomized clinical trials, are needed to confirm our observations. Some disadvantages, such as the method of general anesthesia or the time-consuming nature of the procedure require further improvement.

REFERENCES


